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Octreotide: drug development of a constrained somatostatin analogue

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The discovery of somatostatin (SRIF) initiated a period of intense activity among endocrinologists and peptide chemists. The availability of synthetic hormone facilitated the detection of a wide range of biological activities and it soon became apparent that inhibition of growth hormone secretion was only one of many actions of pharmacological interest. This broad physiological profile led to speculations that SRIF might be of therapeutic value in the management of various endocrine, metabolic, and gastrointestinal disorders. But it soon became clear that the clinical utility of SRIF was limited on the one hand by its very short biological half-life and on the other because of possible undesired side-effects arising from unspecific inhibition of various physiological functions. Especially inhibition of insulin secretion was considered to be possibly detrimental.

The main task, then, for medicinal chemistry was to find analogues which lacked the disadvantages of native SRIF and intense competition soon broke out among several teams of peptide chemists to design and synthesise the desired analogues.

Rivier and Vale from the Salk Institute provided SAR studies which allowed conclusions to be drawn about the essential residues: by means of systematic deletions they found analogues which retained considerable activity. Stimulating insights came also from the Merck group-potent cyclic and bicyclic analogues containing the essential residues Phe-Trp-Lys-Thr further supported the hypothesis of a beta-turn in the active core. Thus progressively smaller analogues were designed and their work culminated in very potent cyclic hexapeptides which were highly resistant to proteolysis.

In our team, work commenced with a weakly active cystine-bridged hexapeptide containing the active core. By N- and C-terminal exocyclic addition of corresponding structural features deduced from the natural sequence we obtained a series of highly active octapeptide analogues. After careful biological evaluation, we selected the cyclic compound H-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr(ol), code-named SMS 201-995, for further development. This compound, now known as octreotide (Sandostatin®) turns out to have fulfilled most of the criteria we set ourselves at the beginning of a search for a clinically useful somatostatin analogue. Compared with the native hormone, octreotide is more potent, has greater metabolic stability and prolonged duration of action, causes no rebound hypersecretion, has greater selectivity for inhibition of GH secretion, and because of its small size is easy to synthesise on a technical scale.

In numerous clinical studies octreotide has been generally well tolerated and side-effects have been minimal since it has stronger inhibitory effects on pathologically elevated hormone secretion than on basal levels.

Octreotide was recently introduced to the market under the trade name Sandostatin®, thus far in the indications gastrointestinal endocrine tumours and acromegaly. The use of Sandostatin in many other indications is currently under clinical investigation. Promising new approaches in the treatment of malignant diseases seem possible, either via direct effects on somatostatin-receptor-positive tumour cells or probably via indirect effects on certain growth factors.

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